Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 7597
215 652 5000
Fax 610 397 2516

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Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

MERCK
Research Laboratories

Re: Draft Guidance for Industry on IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format; Availability

Merck & Co., Inc., is a worldwide research-intensive company that leads the ethical U.S. pharmaceutical industry in discovery, development, production and marketing of human and animal health products and specialty chemicals. Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations dedicated to improving human health, animal health, and agriculture. Through a complex and multidisciplinary process, MRL involves scientists from every technical discipline in targeting, discovering, and testing compounds to conquer today's unique diseases. MRL's innovation strategy includes research and development of many compounds or potential drug candidates at one time. The MRL R&D process (for human drugs) can be separated into three main stages: basic research, followed by developmental research and, finally, human clinical/veterinary research.

Today's R&D is a highly risk-intensive worldwide business. Commercialization of products in many countries directly depends upon a regulatory climate that foster timely development and government policies that are consistent and socially responsible, but do not add extra uncertainty to the research process. Worldwide R&D programs must also be responsive to international economic and social concerns. Indeed, we are also concerned about inconsistencies among regulatory regimes in different countries that may require unusual or duplicative research testing.

For these reasons, we are very interested in and well qualified to comment on this FDA Draft guidance entitled, "IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing and Controls Content and Format". The purpose of the guidance is to provide recommendations on the chemistry, manufacturing and controls documentation (CMC), including microbiology documentation that should be submitted for Phase 2 and 3 of IND's. We have reviewed the document in detail and offer the following comments for consideration as the guidance document evolves.

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General Comments on Introduction and Background

The draft FDA guidance emphasizes that the focus is on issues pertaining to safety, however, the guidance recommends a considerable level of detail on nonsafety issues to be provided in the Phase 3 information. The guidance provides only minimal definition of which issues the Agency considers to be "CMC safety data and information" (84-88)[1]. In general, the information requirements in this guidance for Phase 3 INDs are the same as those for an NDA, with the exception that the IND information can be spread out over several amendments or annual updates, whereas, the NDA is a historical compilation of data supporting final product image proposed for marketing which are provided in one document. It is unclear as to why the Agency is requesting this level of detail, prior to the NDA review. It would be helpful to know if the provision of this level of detail is for purposes of an earlier review of the CMC information to be contained in a NDA (i.e. rolling submission, "pre-NDA") or is it considered necessary to evaluate the safety of Phase 3 formulations. In general, the Phase 3 requirements are defining what should be present by the time Phase 3 is completed and the NDA filing is imminent. While these requirements are useful in preparing the documentation necessary for the NDA, it is our hope that this guidance document, with the current requirements, will not be used as a "checklist" for Phase 2 and 3 IND's.

The timing for submission of "supplementary information" (34-35) is not clear. One interpretation could be that the listed requirements could be obtained during Phase 3 development and not submitted until the NDA. Lines 72-73 and 81-83 state that these data can be submitted when generated during Phase 3 as summary annual reports, but this appears to be a rolling NDA submission. Generally, IND amendments are not submitted for supplementary information updates, but rather are submitted to cover drug substance synthesis changes, safety issues and formulation changes.

III. Phase 2

A. Drug Substance

The guidance requires that reagents (including solvents and catalysts), equipment (e.g. fermenters, columns), and provisions for monitoring and controlling conditions used in each step should be identified (151-153). This required information is exceeding the current expectations. At early stages of development, definitive process equipment is still being identified and it is therefore difficult to commit to specific equipment. The requested information on process controls is contradictory. It states that "To the extent possible in Phase 2, sponsors should document that the manufacturing process is controlled at predetermined points...". However, in the next sentence (160-162), it is acknowledged that in-process controls may still be in development.

The guidance states that certificates of analysis (COA) of clinical trial material prepared since the filing of the original IND should be provided (193, 415). We propose providing batch data in tables which should be sufficient to show representative results of material made since the original IND, rather than individual certificate of analysis.

[1] Reference to specific lines of the draft guidance are included in parenthesis.

The guidance document states that a stability protocol should be submitted which includes a list of tests, analytical procedures, sampling time points for each of the tests and the expected duration of the stability program (217). Providing a stability protocol in Phase 2 is considered excessive since it is typically not provided until the NDA.

B. Drug Product

The guidance document recommends that a batch formula be provided (234). It should be noted that the batch size used to prepare these formulations will vary depending on the clinical supply requirements and, as such, is not considered an effective parameter to evaluate the safety of these formulations.

The guidance recommends that information regarding excipients not included in previously approved drug products be equivalent to that for new drug substance (248). We propose that where available, a DMF reference is provided, but in lieu of this, information from the supplier, related to the safety of the components in the excipients should be provided. Additional information is considered unnecessary, prior to the NDA.

The guidance states that certificates of analysis (COA) of clinical trial material should be provided (286). As previously mentioned, providing representative batch analysis data in tables should be sufficient to show test results of a clinical trial formulation, rather than a certificate of analysis.

The guidance document states that a stability protocol should be submitted which includes a list of tests, analytical procedures, sampling time points for each of the tests and the expected duration of the stability program (299-301). Providing this level of detail in a stability protocol in Phase 2 is considered excessive, since it is typically not provided until the NDA. The duration of the stability program is based on the length of the on-going clinical studies, and may therefore change after initiation of the study. Additionally, it should be clarified that stability data from material that is representative of Phase I supplies may be provided (303-304). This section of the document also states that stress testing (e.g. photostability) should be conducted on the drug product (305). This information is usually provided in the NDA, not in the IND. Stress testing should be recommended "as applicable", based on the characteristics of the drug substance or dosage form".

IV. Phase 3/Pivotal Study

A. Drug Substance

The requirements for raw material minimum acceptable purity (347-350) is still being defined at this stage of development. Although vendors have been identified, many are still optimizing their processes and there are some variances in the purity of material received from them. This information is typically not provided until the NDA submission. The guidance states (352-354) that in critical cases, a full description of the manufacturing process may also be needed. This statement should be clarified describing what is meant by critical cases. In addition, it is unclear if a full description of the preparation of complex reagents is required since these are generally not provided until the NDA.

General guidelines are given for the content of drug substance process description (362-367). Some of the information requirements appear to be excessive. The range of batch size should be clarified to specify the range of batches made to date. It is unclear if the range of batch size is meant to include proposed batch sizes for Phase 3 studies and beyond, such as commercial production. The batch size may vary during development depending upon the availability of pilot scale equipment and the need to mimic proposed factory operations with specific equipment and thus specifying a range may limit flexibility during development. The text "final recrystallization" (363) should be replaced with "final isolation" since not all drug substances are routinely recrystallized.

The type of reaction vessel is also requested as relevant information to be presented in the process description (364). This information would be more useful in a NDA process description where the typical example of practice is given. During development, the drug substance is manufactured in "flexible use" pilot plant equipment whereas during routine production of marketed material, dedicated process equipment is used. It is thus difficult and considered an excessive requirement to specify equipment during this stage of drug substance manufacturing.

The guidance document also requires that acceptance criteria (372-378) and validation data be available upon request from intermediate testing and in-process testing. The acceptance criteria are under development during this time period in which the full extent of the drug substance process to reject impurities present in various intermediates is being defined. The requirement of validation data for intermediate tests is considered excessive during this stage of development.

The guideline states that (408-409) "Impurities should be identified, qualified and quantified, as appropriate. Suitable limits based on manufacturing experience should be established". Specifications during the IND stage (408-411) are not typically established solely ~~on~~ manufacturing experience but rather a combination of manufacturing experience, safety data and ICH recommendations. The draft guideline states that "suitable microbial limits should be established for nonsterile products and changes in previously reported limits should be reported" (410). Microbial limits are not usually established for nonsterile products unless the material has been shown to support microbial growth.

Currently, while the tabulated stability data is presented in an IND, the extensive details of the stability protocol (433) are not presented until the NDA filing. The inclusion of individual stability data points together with representative chromatograms and spectra is excessive.

B. Drug Product

The guidance document recommends that a batch formula be provided (460). The batch size used to prepare these formulations will vary depending on the clinical supply requirements and, as such, is not considered an effective parameter to evaluate the safety of these formulations.

The guidance recommends a full description of the characterization, manufacture, control, analytical procedures and acceptance criteria be provided for non-compendial excipients (473). As previously mentioned where available, a DMF reference is provided, but in lieu of this, information related to the safety of the components in the excipients should be provided. Additional information is considered unnecessary, prior to the NDA.

The guidance document states that the degradation products should be identified and qualified (510). This statement should be clarified by referring to the ICH Q3B Guideline. Where possible, it is recommended that the Agency refer to the ICH Guidelines.

The guidance states that the manufacturer and supplier of the container closure system components should be provided (523). Except for cases where novel components are being utilized for clinical studies, providing this information may unnecessarily limit flexibility in packaging clinical supplies. The container closure system used for clinical supplies is not necessarily the same as for the Market Container Stability Studies or marketed product.

The guidance document states that a stability protocol should be submitted which includes sampling time points for each of the tests and the expected duration of the stability program (538-540). The sampling time points duration of the stability program are based on the length of the on-going clinical studies, and may therefore change after initiation of the study and are not appropriate for inclusion in the IND. This section of the document also states that stress testing (e.g. photostability) should be conducted on the drug product (535). This information is usually provided in the NDA, and is considered excessive for the IND. Stress testing should be recommended "as applicable", based on the characteristics of the drug substance or dosage form. The statement regarding dissolution profiling in physiologically relevant media with reasonable speeds of agitation, where appropriate (541-542) is vague and should be clarified.

This document provides recommendations for data to be generated during the various phases of development, but the timing for submission of much of this information should be "prior to or at NDA filing". In general, the level of detail recommended in the guidance document for Phase 3 studies is considered excessive and more appropriate for a New Drug Application.

We trust that these comments will be considered in further development of the draft guidance.

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.
Senior Director
Regulatory Affairs

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